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SYNTHESIS OF 3-AMINOALKYL SUBSTITUTED CARBAPENEMS VIA A PHOSPHORANE INTERMEDIATE

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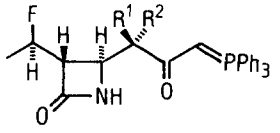
Abstract: Reaction of azetidinone phosphoranes 1 with aldehyde 8 gave the olefins 4, which were converted into carbapenem esters 6 in 4 steps. Hydrogenation of 6 gave the title compounds.

In our search for carbapenems with better chemical and biological stability[2] we wanted to synthesize carbapenems substituted in the 3-position with aliphatic side chains, preferably provided with a basic functionality. The four general[3] syntheses known for this class of compounds have their limitations: In the two Merck procedures[4] the variable side chain is introduced as Grignard or cuprate reagent onto an azetidinone aldehyde or thiol ester, which limits the choice of side chain substituent. The other two methods from Sanraku Ocean chemists[5] and from us[2b] have the advantage that derivation occurs at a late stage in the synthesis on a bicyclic intermediate, but they only serve to introduce side chains with strongly electron-withdrawing groups on the α-carbon atom.

Since very few reactions can be performed on the bicyclic carbapenem or 3-oxo-carbapenam system without opening at least one of the two rings[6] we preferred to introduce the variable side chain on an azetidinone intermediate. As it turns out, the azetidinone phosphorane 1a[7] is a very suitable intermediate: not only is it chemically very stable, but also, its low basicity allows Wittig reaction with aldehydes that can have a wide range of substituents including acidic ones such as amides and alcohols. Phosphorane 1a (mp. 152-155°C) was easily prepared from the previously synthesized bromo-ketone 2[2c] (see Scheme and Reaction conditions) in 90% yield. Optically active 1b (mp. 164-165°C) was synthesized in a more direct way by reacting ester 3b with 2.5 eq of $Ph_3P{=}CH_2$[8] in THF at -20°C. Reaction of 1a with PhCHO in refluxing toluene gave the expected olefin 4a (only trans, mp. 112-114°C) in 60% yield. Woodward's elaboration[9] via phophorane 5a (48%) gave carbapenem 6a (61%) as a yellow solid (mp. 155-160°C). Short (20 min.) hydrogenation of 6a did not produce the expected carbapenem potassium salt, instead, we only found carbapenam 7 as a mixture of 2ß,3ß (22%) and 2α,3α (6%) isomers[10] which was separated by RP-18 chromatography (H_2O-CH_3CN, 0-10%). In spite of this discouraging result, we proceeded by reacting 3a with protected aminoaldehyde 8[11]. This reaction took place at much lower temperatures (60-80°C) than the one with benzaldehyde. Presumably, the reaction is catalyzed by intramolecular hydrogen bonding between the amide NH and the developing alkoxy anion in the transition state.



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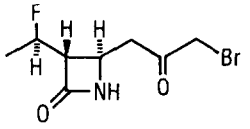
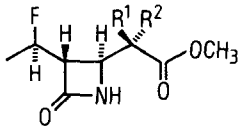


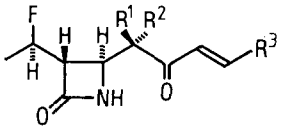
(±)2



3

1. a. $R^1 = R^2 = H$, (±)
   b. $R^1 = R^2 = H$, (+)
   c. $R^1 = H$, $R^2 = CH_3$, (+)
   d. $R^1 = CH_3$, $R^2 = H$, (-)

3. b. $R^1 = R^2 = H$, (+)
   c. $R^1 = H$, $R^2 = CH_3$ (+)
   d. $R^1 = CH_3$, $R^2 = H$ (-)



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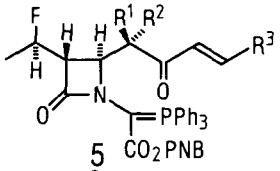

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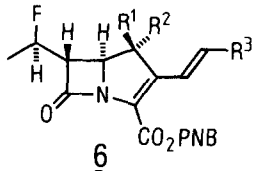
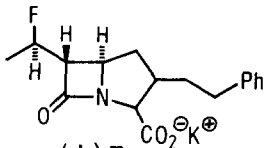
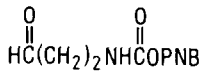


6

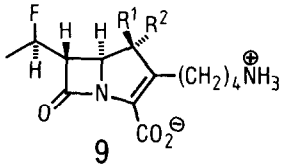
4,5,6. a. $R^1 = R^2 = H$, $R^3 = Ph$, (±)
b. $R^1 = R^2 = H$, $R^3 = CH_2CH_2NHCO_2PNB$, (±)
c. $R^1 = H$, $R^2 = CH_3$, $R^3 = CH_2CH_2NHCO_2PNB$, (opt.act.)
d. $R^1 = CH_3$, $R^2 = H$, $R^3 = CH_2CH_2NHCO_2PNB$, (opt.act.)



(±)7

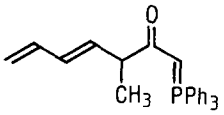


8

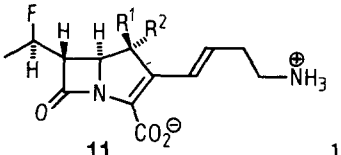


9

9. a. $R^1 = R^2 = H$, (±)
   b. $R^1 = H$, $R^2 = CH_3$, (opt.act.)
   c. $R^1 = CH_3$, $R^2 = H$, (opt.act.)



(±)10



11

11. a. $R^1 = H$, $R^2 = CH_3$, (opt.act.)
    b. $R^1 = CH_3$, $R^2 = H$, (opt.act.)

Reaction conditions:

2 → 1a:	i. PPh_3, CH_2Cl_2 ii. $NaHCO_3$, H_2O
3 → 1:	$Ph_3\overset{+}{P}CH_3Br^-$, n-BuLi, THF -78^oC -20^oC
1 → 4:	RCHO, benzene or toluene, reflux
4 → 5:	i. $PNBO_2CCH(OH)_2$, benzene, azeotropic reflux. ii. $SOCl_2$, Et_3N, THF, -20^oC. iii. Ph_3P, THF, RT
5 → 6:	Toluene, reflux
6 → 7,9,11:	H_2, Pd/C (10%), EtOAc, phosphate buffer pH 7
1a → 10:	i. 2.5 eq LDA, 5 eq HMPA, THF, -78^oC. ii. CH_3I -78 0^oC

The resulting olefin 4b (only trans, mp. 118-121°C, 93%) was converted to the phosphorane 5b (43%) which was cyclized to carbapenem 6b (mp 143-146°C, 55%). Fortunately, hydrogenation of 6b gave 3-(4-aminobutyl)-carbapenem 9a in 84% yield after RP-18 chromatography and lyophilization.

Merck chemists discovered that introduction of a 4ß-methyl group on 3-thio substituted carbapenems greatly improved their stability towards renal dehydropeptidase[12]. Synthesis of 9c therefore seemed a worthwile goal, particularly since 9a had insufficient DHP-stability. Direct methylation (2.5 eq. LDA, HMPA, CH_3I) of 1a did not give (±) 1c,d; all we could isolate (63 % yield) was the unexpected elimination product 10. Better results were obtained when a 2:1 mixture of 3c and 3d[13] was treated with 2.5 eq. of $Ph_3P{=}CH_2$ in THF at -20^oC overnight. After work-up and medium pressure chromatography we obtained pure α-methyl-phosphorane 1c[14] (mp 153-155°C, 27%), a mixture of 1c and 1d (9%), and pure 3d (27%) uncontaminated by 3c. Being more interested in the ß-methyl-phosphorane 1d we tried to equilibrate 1c to 1d (LDA, -78^oC; HOAc, -78^oC). As this was unsuccessful we reacted recovered 3d once more with $Ph_3P{=}CH_2$. This gave phosphoranes (1c:1d = 19:81) in 47% yield. Eventually, 1d was obtained pure after rechromatography and crystallization (CH_2Cl_2-i-Pr_2O, mp. 78-82°C) in 7% overall yield. Further elaboration of 1c and 1d to 6c and 6d proceeded uneventfully; no epimerization occurred in any of these steps and deliberate attempts to epimerize 4c,5c and 6c to their ß-methyl counterparts all remained fruitless. Hydrogenation of 6c produced a mixture of 9b (15%) and 11a (21%) which was separable on RP-18 (H_2O-CH_3CN, 0-10%) allowing us to evaluate the effect of the conjugated double bond on biological activity. Hydrogenation of 6d likewise produced a mixture of 9c (44%) and 11b (16%) but we were unable to separate this. Prolonged hydrogenation produced pure 9c in 42% yield. Full experimental details and biological activity of these compounds will be published elsewhere.

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3. For a synthesis of a 3-(2-aminoethyl)-carbapenem by a non-general method see: K. Fujimoto, Y. Iwano and K. Hirai, Tetrahedron Lett. 1985, 89.

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5. T. Yoshioka, K.-I. Yamamoto, Y. Shimauchi, Y. Fukagawa, and T. Ishikura, J.Chem.Soc. Chem.Commun., 1984, 1513.

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7. Selected spectral data (NMR spectra in $CDCl_3$ or D_2O, UV's and rotations in CH_2Cl_2 or H_2O): 1a: ^{1}HNMR: δ 4.95(1H,ddq,J=49.0,7.0,6.3Hz,HCF), 3.99(1H,ddd,J=9.5,4.1,2.2Hz, H-4), 3.72(1H,br d,J=26.5Hz,HCP), 3.00(1H,dddd,J=20.2,7.0,2.2,1.4Hz,H-3), 2.82 and 2.55(2H,ABX,J_{AB}=14.4Hz,J=9.5,4.1Hz,CH_2), 1.42(3H,dd,J=24.4,6.3Hz,CH_3). 1b: UV: λ_{max}= 265,272,294 nm, $[\alpha]_D^{21}$= +58.7°. 1c: ^{1}H NMR: δ 3.67 (1H,dd,J=10.5,2.0Hz,H-4), 1.24 (3H, d,J=6.8Hz,α-CH_3), $[\alpha]_D^{21}$= +58.4°. 1d: ^{1}H NMR: δ 3.86(1H,dd,J=4.9,2.4Hz,H-4). 1.22 (3H, d,J=6.5Hz,β-CH_3), $[\alpha]_D^{21}$= -10.9°. 4a: ^{1}H NMR: δ 7.58(1H,d,J=16.0Hz,=CH), 6.75 (1H,d, J=16.0Hz,=CH). 4b: ^{1}H NMR: δ 6.84(1H,dt,J=16.1,7.1Hz,=CH), 6.18(1H,d,J=16.1Hz, =CH). 4c: ^{1}H NMR: δ6.89(1H,dt,J=16.3,7.0Hz,=CH), 6.25(1H,d, J=16.3Hz,=CH). 4d: ^{1}H NMR: δ 6.87(1H,dt,J=15.8,7.0Hz,=CH), 6.21(1H,d,J=15.8Hz,=CH). 6a: IR(KBr): 1796,1701 cm^{-1}. 6b: IR(KBr): 1789,1709 cm^{-1}. 6c: IR(KBr): 1800,1710 cm^{-1},$[\alpha]_D^{21}$= -54.6°. 6d: IR (CH_2Cl_2): 1776,1726 cm^{-1},$[\alpha]_D^{21}$= -30.8°. 7(2α,3α): ^{1}H NMR: δ 4.36(1H,d,J=7.2Hz,C-2). 7(2β,3β): ^{1}H NMR: δ 3.82(1H,d,J=8.0Hz,C-2). 9a: UV: λ_{max}=267 nm, IR(KBr): 1759 cm^{-1}. 9b: UV: λ_{max}=243,267 nm, IR(KBr): 1774 cm^{-1}. 9c: UV: λ_{max}=266 nm, IR(KBr): 1751 cm^{-1}. 10: ^{1}H NMR: δ 6.39(1H,ddd,J=17.0,10.3,10.0Hz,H-6), 6.16(1H,dd,J=15.3, 10.0Hz, H-5), 5.99(1H,dd,J=15.3,7.5Hz,H-4), 5.11(1H,dd,J=17.0,1.5Hz,H-7Z), 4.98(1H, dd, J= 10.3,1.5Hz,H-7E), 3.69(1H,br d,J=26.6,H-1), 3.14(1H,dq,J=7.5,6.8Hz,H-3), 1.30 (3H,d, J=6.8Hz,CH_3). 11a: ^{1}H NMR: δ 6.85(1H,d,J=16.3Hz,=CH), 5.85(1H,dt,J=16.3,7.1Hz, =CH), IR(KBr): 1779 cm^{-1}, UV: λ_{max}=295 nm. 11b: ^{1}H NMR: δ 7.01(1H,d,J=16.4Hz,=CH), 5.97 (1H, dt,J=16.4,7.0Hz,=CH).

8. The presence of LiBr is essential: With phosphorane prepared from $Ph_3P^+CH_3Br^-$ and $NaNH_2$ (Instant ylid, Fluka) no reaction occurred.

9. R. Scartazzini, H. Peter, H. Bickel, K. Heusler, and R.B. Woodward, Helv.Chim.Acta, 1972, 55, 408.

10 For stereochemical assignment see ref 14 in ref 2b.

11. Ethylene glycol protected 3-amino-propionaldehyde was prepared from the bromide (Gabriel), N-protected with $ClCO_2PNB$ and the aldehyde deprotected (dioxane, 0.1 N HCl, reflux).

12. D.H. Shih, F. Baker, L. Cama, and B.G. Christensen, Heterocycles, 1984, 21, 29.

13. From 3b, by treatment with 3 eq of LDA in THF at -78°C, followed by CH_3I. C.P. Mak, unpublished results. See also ref 12.

14. Stereochemical assignment from NOE experiments performed on 6c and 6d: Irradiation at the 4-methyl frequency caused enhancement of the H-5 absorption in 6c and not in 6d.

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